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Potassium Perchlorate, Potassium Iodide, and Propylthiouracil: Promoting Effect on the Development of Thyroid Tumors in Rats Treated with N-Bis(2-hydroxypropyl)-nitrosamine

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The effect of 1000 ppm potassium perchlorate ($KClO_4$), 1000 ppm potassium iodide (KI) or 1000 ppm propylthiouracil (PTU) in the diet on the development of thyroid tumors was studied histologically and biochemically in Wistar rats given a single ip injection of 280 mg of N-bis(2-hydroxypropyl)nitrosamine (DHPN) per 100 g body weight. Basal diet containing 1000 ppm $KClO_4$, 1000 ppm KI or 1000 ppm PTU was given for 19 weeks from week 2 to week 20. The incidence of thyroid adenomas at the end of week 20 of the experiment was 100% (20/20) in rats treated with DHPN followed by $KClO_4$, 85% (17/20) in rats given DHPN followed by KI, 95% (19/20) in rats given DHPN followed by PTU, and 5% (1/20) in rats given DHPN alone. The incidence of thyroid cancers was 100% (20/20) in rats treated with DHPN followed by $KClO_4$, 65% (13/20) in rats treated with DHPN followed by KI and 0% (0/20) in rats treated with DHPN followed by or not followed by PTU. Rats given $KClO_4$, KI or PTU alone and untreated rats had no thyroid tumors. The mean values of TSH in serum were 2.94 ± 0.79 ng/ml in rats treated with DHPN followed by $KClO_4$, 9.40 ± 16.0 ng/ml in rats treated with DHPN followed by KI and 60.94 ± 20.60 ng/ml in rats treated with DHPN followed by PTU. It was confirmed that (1) $KClO_4$, PTU and KI promote the development of thyroid tumor in rats treated with DHPN, (2) the promoting effect of $KClO_4$ or KI is stronger than that of PTU and (3) the value of TSH in serum is not parallel to the promoting effect on the development of thyroid tumor.

Key words: Potassium perchlorate — Potassium iodide — N-Bis(2-hydroxypropyl)nitrosamine — Thyroid tumor

Recently, we have reported the effects of 3-amino-1,2,4-triazole (AT),[1] phenobarbital (Pb),[2-5] propylthiouracil (PTU),[6] and 4,4′-diaminodiphenylmethane (DDPM)[7] in promoting thyroid tumors in rats treated with DHPN. The mechanisms involved are still not clearly understood, though it was suggested that an increased concentration of TSH in serum induced by AT, Pb, PTU or DDPM promotes the develoment of thyroid tumors. Pb stimulates the drug-metabolizing enzymes in the liver[8] and leads to an accelerated turnover of TSH, T4 or T3. AT and PTU inhibit the synthesis of T4 or T3.[9,10] Decreased T4 and T3 in serum stimulate the secretion of TSH.

$KClO_4$ inhibits the transport of iodine from the serum to the thyroid[11,12] and KI inhibits the secretion of T3 and T4,[13,14] while $KClO_4$ and KI both raise the serum TSH.[11-14]

The purpose of the present work was to study the promoting effect on thyroid tumorigenesis of various chemicals that inhibit iodine circulation at different points. This paper compares the histological or biochemical findings in rats treated with DHPN followed by $KClO_4$, KI or PTU.

Abbreviations: $KClO_4$, potassium perchlorate; KI, potassium iodide; PTU, propylthiouracil; DHPN, N-Bis(2-hydroxypropyl)nitrosamine; AT, 3-amino-1,2,4-triazole; Pb, phenobarbital; DDPM, 4,4′-diaminodiphenylmethane; TSH, thyroid-stimulating hormone; T4, 3,5,-3′,5′-tetraiodothyronine; T3, 3,5,3′-triiodothyronine; BD, basal diet.

MATERIALS AND METHODS

Chemicals and Diet DHPN [N-bis(2-hydroxypropyl)nitrosamine, CAS: 53609-64-6; dipropylamine, 2,2′-dihydroxy-N-nitro] (purity 99.8%,

liquid at room temperature) was purchased from Nakarai Chemicals, Kyoto. $KClO_4$ (potassium perchlorate), KI (potassium iodide) and PTU (propylthiouracil) were purchased from Nakarai Chemicals. The basal diet used was CE-1 purchased from Clea Japan Inc., Osaka.

Animals and Experimental Design One hundred and seventy male inbred 6-week-old Wistar rats, purchased from Shizuoka Animal Farm Co., Shizuoka, were given the basal diet. After 1 week, 160 healthy rats, weighting 150–170 g, were divided into 8 groups of 20 rats, and given the basal diet for one week then the basal diet with the following additions: groups 1 and 5 — 1000 ppm $KClO_4$, groups 2 and 6 — 1000 ppm KI, groups 3 and 7 — 1000 ppm PTU from week 2 for 19 weeks and groups 4 and 8 — basal diet for 19 weeks. All rats in groups 1, 2, 3 and 4 received an ip injection of DHPN (280 mg per 100 g body weight) at the beginning of the experiment as an initiator.

The animals were housed in wire cages in an air-conditioned room at 24° and were weighed weekly. All rats survived the experiment. At the end of the 20-week experiment, blood was collected from rats without fasting in each group, for assay of the thyroid-stimulating hormone (TSH). After autopsy by careful macroscopic examination, the thyroid and liver were removed, weighed and fixed in 10% buffered formalin. Serial sections were made of the thyroids of all animals. Sections were routinely stained with hematoxylin and eosin, and specific stains, such as periodic acid-Schiff and Grimelius, were employed in some cases. The thyroid tumors were counted in the largest serial section, using the histological classification of thyroid tumors reported by Napalkov.[15]

Assay of Serum TSH, T4 and T3 Serum concentrations of TSH, T4 and T3 in all rats were measured by radioimmunoassay.

The radioimmunoassay of TSH was carried out according to the outline protocol suggested by Dr. Parlow. Rat-TSH and specific rat-TSH antiserum were provided by Dr. A. F. Parlow (Dept. of Obstetrics and Gynecology, School of Medicine, Harbor General Hospital, California) under the NIADDK Rat Pituitary Hormone Program. TSH (TSH-1-8) was iodinated by the chloramine T method using 1 mCi of ^{125}I (Radiochemical Centre, Amersham), 4 μg of rat TSH in 0.5M phosphate buffer (pH 7.6) and 15 μg of chloramine T. The total reaction volume of 40 μl was incubated for 4 min, and the reaction was stopped by the addition of 250 μg (in 100 μl) of sodium metabisulfate. The labeled TSH was purified on Sephadex G-75 and the purity was checked by paper electrophoresis.

The standard curve for rat TSH-RP2 was set up in quadruplicate tubes covering the range of 50 to 0.3 ng TSH/ml. Unknown samples were assayed in duplicate at two dose levels. Each assay tube was set up as follows: 0.01M phosphate buffer (pH 7.6) with 1% bovine serum albumin (BSA) (0.3 ml), standard TSH or unknown serum diluted 1:1 with buffer (0.2 ml), 100 pg of rat [^{125}I]iodo-TSH in buffer with 0.1% BSA (0.1 ml) and antibody (NIADDK-S5) diluted 1:10000 in buffer with 0.05M EDTA and 0.3% normal rabbit serum (0.2 ml). The tubes were placed briefly on a vortex mixer and incubated for 96 hr at 4°. Donkey antirabbit serum (200 μl, 1:25 dilution, Burroughs Wellcome Laboratories) in assay buffer containing 0.05M EDTA and 0.03% normal rabbit serum was added. The tubes were mixed and incubated for further 24 hr at 4°, before centrifugation at 4° for 30 min. The precipitate was counted in a well scintillation counter. All samples from these experiments were assayed in a single assay batch.

T4 was measured with a Corning T4 radioimmunoassay kit (Corning Medical, Corning Glass Works, Medfield, Mass.) and T3 was measured with a T3 radioimmunoassay II (Dainabot RI Institute, Tokyo).

Results

Mean Body, Thyroid, and Liver Weights The final mean body, thyroid, and liver weights in each group are shown in Table I. There are significant differences between the final mean body weight in group 3 (DHPN and PTU) and that in group 4 (DHPN alone), and between that in group 7 (PTU alone) and that in group 8 (non treated rats). The mean thyroid gland weights in groups 1 (DHPN and $KClO_4$) and 3 (DHPN and PTU) were significantly higher than the mean weight in group 4 (DHPN alone). The mean thyroid gland weights in groups 5 ($KClO_4$ alone) and 7 (PTU alone) were significantly higher than in group 8 (non treated rats). The mean weight of the thyroid glands in group 2 (DHPN and KI) was higher than the mean weight in group 4 (DHPN alone) but not significantly, because there were marked variations in the thyroid weight in group 2 (DHPN and KI) and the standard deviation was very high.

The mean weight of livers in group 3 (DHPN and PTU) was significantly lower than the mean weight in group 4 (DHPN alone). Further, the mean weight of livers in group 7 (PTU alone) was significantly lower than that in group 8 (non treated rats). However the ratio of liver weight to body weight in all the experimental groups was not signifi-

Table I. Mean Weights of Body, Thyroid and Liver in Rats Treated with $KClO_4$, KI and PTU after DHPN

Group	No. of rats	Final body weight (BW) (g)	Thyroid		Liver	
			weight (TW) (g)	TW/BW × 10^4	weight (LW) (g)	LW/BW × 10^2
1. DHPN + $KClO_4$	20	326 ± 23	87 ± 29[a]	2.66 ± 0.94	7.81 ± 0.68	2.4 ± 0.2
2. DHPN + KI	20	312 ± 17	63 ± 61	2.19 ± 2.31	7.46 ± 0.83	2.4 ± 0.2
3. DHPN + PTU	20	146 ± 21[a]	197 ± 47[a]	14.20 ± 3.99[a]	3.96 ± 0.70[a]	2.6 ± 0.6
4. DHPN	20	302 ± 18	16 ± 1	0.56 ± 0.06	7.68 ± 0.84	2.5 ± 0.2
5. $KClO_4$	20	340 ± 17	33 ± 3[b]	0.99 ± 0.06[b]	7.81 ± 0.53	2.3 ± 0.1
6. KI	20	319 ± 20	23 ± 8	0.72 ± 0.25	7.73 ± 0.45	2.4 ± 0.1
7. PTU	20	208 ± 40[b]	175 ± 27[b]	7.56 ± 3.54[b]	4.70 ± 0.46[b]	2.3 ± 0.5
8. BD	20	318 ± 18	17 ± 1	0.54 ± 0.05	7.60 ± 0.64	2.4 ± 0.2

Abbreviations: see title page.
Values are means ± SD.
a) Statistically significant compared to group 4 by Student's *t*-test ($P < 0.05$).
b) Statistically significant compared to group 8 by Student's *t*-test ($P < 0.05$).

Table II. Incidences of Thyroid Tumor in Rats Treated with $KClO_4$, KI and PTU after DHPN

Group	No. of rats	No. of rats with adenoma (%)	No. of rats with cancer (%)
1. DHPN + $KClO_4$	20	20 (100)[a]	20 (100)[a]
2. DHPN + KI	20	17 (85)[a]	13 (65)[a]
3. DHPN + PTU	20	19 (95)[a]	0
4. DHPN	20	1 (5)	0
5. $KClO_4$	20	0	0
6. KI	20	0	0
7. PTU	20	0	0
8. BD	20	0	0

Abbreviations: see title page.
a) Statistically significant compared to group 4 by χ^2-test ($P < 0.05$).

cantly different from that in group 8 (non treated rats).

Incidence of Thyroid Tumors The incidence of thyroid tumors in each group is summarized in Table II. The incidence of thyroid adenoma was 100% (20/20) in group 1 (DHPN and $KClO_4$), 85% (17/20) in group 2 (DHPN and KI), 95% (19/20) in group 3 (DHPN and PTU), 5% (1/20) in group 4 (DHPN alone), and 0% in groups 5 ($KClO_4$ alone), 6 (KI alone), 7 (PTU alone), and 8 (non treated rats). The incidences of thyroid adenomas in rats treated with DHPN followed by $KClO_4$, KI or PTU are significantly higher than that in rats treated with DHPN alone. Incidences of thyroid cancers were 100% (20/20) in group 1 (DHPN and $KClO_4$), 65% (13/20) in group 2 (DHPN and KI), and 0% in groups 3 (DHPN and PTU), 4 (DHPN alone), 5 ($KClO_4$ alone), 6 (KI alone), 7 (PTU alone), and 8 (non treated rats). The incidence of thyroid cancers in rats treated with DHPN followed by $KClO_4$ or KI is significantly higher than that in rats treated with DHPN alone or followed by PTU.

Histological Analysis of Thyroid Tumors Histological types and the number of thyroid tumors in each group are summarized in Table III. Adenomas or cancers were divided into three histological types, follicular, papillary, and solid. Most adenomas in groups

Table III. Numbers of Thyroid Tumors in Rats Treated with $KClO_4$, KI and PTU after DHPN

Group	No. of rats	Hyperplasia		Adenoma			Carcinoma		
		Cystic	Follicular	Follicular	Papillary	Solid	Follicular	Papillary	Solid
1. DHPN + $KClO_4$	20	43	199	218	19	9	4	4	23
2. DHPN + KI	20	111	28	91	17	0	3	2	19
3. DHPN + PTU	20	164	116	42	3	3	0	0	0
4. DHPN	20	8	0	0	1	0	0	0	0
5. $KClO_4$	20	0	1	0	0	0	0	0	0
6. KI	20	0	0	0	0	0	0	0	0
7. PTU	20	0	0	0	0	0	0	0	0
8. BD	20	0	0	0	0	0	0	0	0

Abbreviations: see title page.

Table IV. Concentrations of Serum TSH, T4, and T3 in Rats Treated with $KClO_4$, KI and PTU after DHPN

Group	No. of rats	TSH (ng/ml)	T4 (μg/dl)	T3 (ng/ml)
1. DHPN + $KClO_4$	20	$2.94 \pm 0.79^{*}$	$2.46 \pm 0.33^{*}$	81.26 ± 10.24
2. DHPN + KI	20	9.40 ± 16.02	2.69 ± 0.83	75.30 ± 10.99
3. DHPN + PTU	20	$60.94 \pm 20.60^{**}$	$1.01 \pm 0.03^{**}$	$65.25 \pm 5.18^{**}$
4. DHPN	20	2.25 ± 1.44	3.47 ± 0.50	90.67 ± 11.52
5. $KClO_4$	20	$2.22 \pm 0.99^{*}$	2.73 ± 0.70	80.13 ± 12.51
6. KI	20	0.94 ± 0.33	3.61 ± 0.44	87.97 ± 11.79
7. PTU	20	$61.00 \pm 19.00^{**}$	$1.13 \pm 0.11^{**}$	$62.00 \pm 6.83^{**}$
8. BD	20	1.01 ± 0.35	3.56 ± 0.66	80.75 ± 3.77

Abbreviations: see title page.
* Statistically significant compared to group 8 by Student's t-test ($P < 0.05$).
**Statistically significant compared to group 8 by Student's t-test ($P < 0.01$).

1 (DHPN and $KClO_4$), 2 (DHPN and KI), and 3 (DHPN and PTU) were of follicular type. Most carcinomas in groups 1 (DHPN and $KClO_4$) and 2 (DHPN and KI) were solid.

Histological Findings in Non-tumorous Areas of the Thyroid Gland Histological findings in the non-tumorous areas of the thyroid gland are summarized in Table III. There was more cystic hyperplasia in group 3 (DHPN and PTU) than in the other groups. There was more follicular hyperplasia in group 1 (DHPN and $KClO_4$) than in the other groups. Histological changes other than focal hyperplasia in the non-tumorous areas were diffused small follicles in groups 1 (DHPN and $KClO_4$), 3 (DHPN and PTU), 5 ($KClO_4$ alone), and 7 (PTU alone) and diffused large follicles in groups 2 (DHPN and KI) and 6 (KI alone). Flat follicular epithelium was seen in the central area of the thyroids in group 6 (KI alone).

Radioimmunoassay of TSH, T4, and T3 in Serum Serum concentrations of TSH, T4, and T3 in each group are summarized in Table IV. The concentrations of serum TSH in groups 1 (DHPN and $KClO_4$), 3 (DHPN and PTU), 5 ($KClO_4$ alone), and 7 (PTU alone) were significantly higher than in group 8 (non treated rats). In group 2 (DHPN and KI), it was higher than in group 8 (non treated rats), but not significantly. In group 6 (KI alone), it was lower than in group 8 (non treated rats). The concentrations of serum T4 in groups 1 (DHPN and $KClO_4$), 3 (DHPN and PTU), and 6 (KI alone) were significantly lower than in group 8 (non treated rats). In groups 2 (DHPN and KI) and 5 ($KClO_4$ alone) they were lower than in group 8 (non treated rats), but not significantly. In

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Papillary	Solid
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group 7 (PTU alone), it was not lower than in group 8 (non treated rats). The concentrations for serum T3 in groups 3 (DHPN and PTU) and 7 (PTU alone) were significantly lower than in group 8 (non treated rats).

Discussion

Promotion of thyroid tumors by PTU in rats treated with DHPN has been described in a previous report.[6] In the present studies PTU increased the incidence of thyroid adenomas significantly but did not increase thyroid cancers in rats treated with DHPN. $KClO_4$ and KI significantly increased the incidence of thyroid adenomas and cancers in rats treated with DHPN.

Histological findings in the thyroids of rats treated with PTU or $KClO_4$ showed diffuse hyperplasia consisting of small follicles. The epithelium of the follicles was swollen. There were few colloids in the follicles. The non tumorous area of thyroids in rats treated with DHPN followed by PTU showed cystic follicles with epithelial damage and fibrosis. There were few colloids in the follicles. It has been reported that PTU inhibits T4 and T3 synthesis by the inhibition of the peroxidase reaction.[10] The non tumorous area of thyroids in rats treated with DHPN followed by $KClO_4$ showed no cystic follicles, no epithelial damage and no fibrosis except for some small follicles. They showed diffuse small follicles and few colloids in the follicles. It has been reported that $KClO_4$ inhibits iodine intake.[11] The non tumorous area of thyroids in rats treated with DHPN followed by KI showed no epithelial damage, no fibrosis and no diffuse small follicles. It has been reported that KI inhibits the secretion of T4 and T3.[13,14] PTU induced follicular cell injury but $KClO_4$ and KI did not.

The increased concentration of serum TSH caused by PTU is due to the decrease of T4 or T3.[16] In the present studies, the concentration of serum TSH in rats treated with DHPN followed by PTU was higher than that in rats treated with DHPN followed by $KClO_4$ or KI and the concentrations of serum T4 and T3 in rats treated with DHPN followed by PTU were lower than in rats treated with $KClO_4$ or KI. The concentration of serum TSH in rats treated with DHPN followed by KI was higher than in rats treated with DHPN followed by $KClO_4$. The standard deviation of serum TSH in rats treated with DHPN followed by KI was larger than in rats treated with DHPN followed by $KClO_4$. It has been reported that the effects of KI on the concentration of serum TSH are inconsistent.[16]

In the present studies, the concentration of serum TSH in rats treated with DHPN followed by $KClO_4$ was lower than that in rats treated with DHPN followed by PTU or KI and the incidence of thyroid tumors in rats treated with DHPN followed by $KClO_4$ was higher than in rats treated with DHPN followed by PTU or KI.

It is suggested that the promotion of thyroid tumorigenesis by $KClO_4$ is due to the high concentration of serum TSH, and there is no severe damage to follicular cells.

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